Claims

1. An isolated nucleic acid molecule, comprising:

(a) nucleic acid molecules which hybridize under stringent conditions to a molecule selected from the group consisting of the nucleic acid of SEQ ID NO:7, the nucleic acid of SEQ ID NO:17, and the nucleic acid of SEQ ID NO:19, and which code for a CNREB-2 polypeptide,

(b) deletions, additions and substitutions of (a) which code for a respective CNREB-2 polypeptide,

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

2. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule comprises SEQ ID NO:17.

3. The isolated nucleic acid molecule of claim 1, wherein the isolated nucleic acid molecule is the nucleic acid molecule of SEQ ID NO:17, or a fragment thereof.

4. An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of nucleic acid molecule selected from the group consisting of the nucleic acid of SEQ ID NO:7, the nucleic acid of SEQ ID NO:17, and the nucleic acid of SEQ ID NO:19,

(b) complements of (a),

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from the sequence group consisting of

(1) sequences described in SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:16,

(2) complements of (1), and

(3) fragments of (1) and (2).

5. The isolated nucleic acid molecule of claim 4, wherein the sequence of contiguous nucleotides is selected from the group consisting of:

(1) at least two contiguous nucleotides nonidentical to the sequence group,

(2) at least three contiguous nucleotides nonidentical to the sequence group,

(3) at least four contiguous nucleotides nonidentical to the sequence group,

(4) at least five contiguous nucleotides nonidentical to the sequence group,

(5) at least six contiguous nucleotides nonidentical to the sequence group,

(6) at least seven contiguous nucleotides nonidentical to the sequence group.

6. The isolated nucleic acid molecule of claim 4, wherein the fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides, 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, and 200 nucleotides.

7. The isolated nucleic acid molecule of claim 4, wherein the molecule encodes a polypeptide which is immunogenic.

8. An expression vector comprising the isolated nucleic acid molecule of claims 1, 2, 3, 4, 5, 6, or 7 operably linked to a promoter.

9. An expression vector comprising the isolated nucleic acid molecule of claim 4 operably linked to a promoter.

10. A host cell transformed or transfected with the expression vector of claim 8.

11. A host cell transformed or transfected with the expression vector of claim 9.

12. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, or 3, wherein the polypeptide, or fragment of the polypeptide, has CNREB-2 activity.

13. The isolated polypeptide of claim 12, wherein the isolated polypeptide is encoded by the isolated nucleic acid molecule of claim 2.

14. The isolated polypeptide of claim 13, wherein the isolated polypeptide comprises a polypeptide having the sequence of amino acids 1-434 of SEQ ID NO:18.

15. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2, or 3, wherein the polypeptide, or fragment of the polypeptide, is immunogenic.

16. The polypeptide of claim 15, wherein the fragment, or portion of the fragment, binds to a human antibody.

17. An isolated binding polypeptide which binds selectively a polypeptide encoded by the isolated nucleic acid molecule of claim 1, 2 or 3.

18. The isolated binding polypeptide of claim 17, wherein the isolated binding polypeptide binds to a polypeptide having the sequence of amino acids of SEQ ID NO:18.

19. The isolated binding polypeptide of claim 18, wherein the isolated binding polypeptide is an antibody or an antibody fragment selected from the group consisting of a Fab fragment, a $F(ab)_2$ fragment or a fragment including a CDR3 region selective for the polypeptide having the sequence of amino acids of SEQ ID NO:18.

20. An isolated polypeptide comprising a fragment of the polypeptide of claim 12 of sufficient length to represent a sequence unique within the human genome and identifying a polypeptide that has CNREB-2 activity, provided that the fragment excludes a sequence of contiguous amino acids encoded by an isolated nucleic acid of SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:16.

21. A method for isolating nucleic acid molecules encoding polypeptides having CNREB-2 activity, comprising:

(a) providing a nucleic acid molecule comprising SEQ ID NO:17, or a fragment of at least 8 contiguous nucleotides thereof,

(b) using the nucleic acid molecule of (a) as a probe to obtain under stringent screening conditions a nucleic acid molecule encoding a polypeptide which is a candidate having CNREB-2 activity,

(c) expressing in a host cell the isolated nucleic acid molecule obtained in (b) to generate the polypeptide, and measuring CNREB-2 activity of the expressed polypeptide, the presence of such activity being indicative of an isolated nucleic acid encoding a polypeptide with CNREB-2 activity.

22. A method for decreasing renin expression in a mammalian cell which expresses renin, comprising:

contacting the mammalian cell with a CNREB-1 inhibitor in the cell in an amount effective to decrease renin expression in the mammalian cell.

23. The method of claim 22, wherein said contacting the mammalian cell with a CNREB-1 inhibitor occurs *in vitro*.

24. The method of claim 22, wherein said contacting the mammalian cell with a CNREB-1 inhibitor occurs *in vivo*.

25. The method of claim 22, wherein the CNREB-1 inhibitor is a nucleic acid.

26. The method of claim 25, wherein the nucleic acid is an antisense nucleic acid or a dominant negative nucleic acid of a CNREB-1 nucleic acid selected from the group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5 and the nucleic acid of SEQ ID NO:6.

27. The method of claims 22-26, further comprising co-administering an adenylate cyclase inhibitor in an amount effective to decrease renin expression in the mammalian cell.

28. A method for decreasing CNREB-1 activity in a subject, comprising:

administering to a subject in need of such treatment a CNREB-1 inhibitor in an amount effective to decrease CNREB-1 activity in the subject.

29. The method of claim 28, wherein the amount is sufficient to decrease CNREB-1 activity below normal baseline levels.

30. The method of claim 28, wherein the subject has an adverse cardiovascular condition.

31. The method of claim 28, wherein the subject has hypertension.

32. The method of claim 28, wherein the subject has congestive heart failure.

33. The method of claim 28, wherein the CNREB-1 inhibitor is a nucleic acid.

34. The method of claim 33, wherein the nucleic acid is an antisense nucleic acid or a dominant negative nucleic acid of a CNREB-1 nucleic acid selected from the group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5 and the nucleic acid of SEQ ID NO:6.

35. The method of claims 28-34, wherein the CNREB-1 inhibitor is administered acutely.

36. The method of claims 28-34, wherein the CNREB-1 inhibitor is administered prophylactically.

37. The method of claim 28, further comprising co-administering an agent other than a CNREB-1 inhibitor, wherein the agent is selected from the group consisting of diuretics, antiadrenergic agents, vasodilators, calcium entry blockers, and angiotensin-converting enzyme inhibitors, in an amount effective to decrease CNREB-1 activity in the subject.

38. The method of claim 28, further comprising co-administering an adenylate cyclase inhibitor in an amount effective to decrease CNREB-1 activity in the subject.

39. A method for increasing CNREB-1 activity in a mammalian cell, comprising:

contacting the mammalian cell with a CNREB-1 activator agent in an amount effective to increase CNREB-1 activity in the mammalian cell.

40. The method of claim 39, wherein the CNREB-1 activator agent is a nucleic acid.

41. The method of claim 40, wherein the nucleic acid is selected from the group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5 and the nucleic acid of SEQ ID NO:6.

42. The method of claim 39, wherein the agent is a polypeptide.

43. The method of claim 39, wherein the agent is a polypeptide, or a functional fragment or variant thereof, which is an expression product of the nucleic acid selected from the group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5 and the nucleic acid of SEQ ID NO:6.

44. The method of claim 39, wherein said contacting the mammalian cell with a CNREB-1 activator agent occurs *in vitro*.

45. The method of claim 39, wherein said contacting the mammalian cell with a CNREB-1 activator agent occurs *in vivo*.

46. A method for increasing CNREB-1 activity in a subject, comprising:

administering to a subject in need of such treatment a CNREB-1 activator agent in an amount effective to increase CNREB-1 activity in the subject.

47. The method of claim 46, wherein the CNREB-1 activator agent is a nucleic acid.

48. The method of claim 47, wherein the nucleic acid is selected from the group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5 and the nucleic acid of SEQ ID NO:6.

49. The method of claim 46, wherein the CNREB-1 activator agent is a polypeptide.

50. The method of claim 46, wherein the CNREB-1 activator agent is a polypeptide, or a functional fragment or variant thereof, which is an expression product of the nucleic acid selected from the group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5 and the nucleic acid of SEQ ID NO:6.

51. The method of claim 46, wherein the amount is sufficient to increase CNREB-1 activity above normal baseline levels.

52. The method of claim 46, wherein the CNREB-1 activator agent is administered acutely.

53. The method of claim 46, wherein the CNREB-1 activator agent is administered prophylactically.

54. The method of claim 46, further comprising co-administering an agent other than a CNREB-1 activator agent, wherein the agent other than a CNREB-1 activator agent is selected from the group consisting of flurocortisone, potassium tablets, vasopressin analogues, somatostatin analogues, beta-blockers, sympathomimetics, dopamine antagonists, and venoconstrictors, and adenylate cyclase activators.

55. A method for determining the level of CNREB-1 expression in a subject, comprising:

a) obtaining a test sample from the individual,

b) measuring the level of expression of CNREB-1 in the test sample,

c) comparing the measured level of expression of CNREB-1 to a control, to determine the level of CNREB-1 expression in the subject.

56. The method of claim 55, wherein the expression of CNREB-1 in (b) is CNREB-1 mRNA expression.

57. The method of claim 55, wherein the expression of CNREB-1 in (b) is CNREB-1 polypeptide expression.

58. The method of claim 55, wherein an increase in the level of CNREB-1 expression compared to the control is indicative of the subject's susceptibility to developing a renin-angiotensin system mediated disorder.

59. The method of claim 58, wherein the renin-angiotensin system mediated disorder is hypertension.

60. The method of claim 58, wherein the renin-angiotensin system mediated disorder is a cardiovascular disorder.

61. A method for determining a subject's susceptibility to developing a renin-angiotensin system mediated disorder, comprising:

(a) characterizing CNREB-1 nucleic acid sequences in a test sample, wherein the test sample is obtained from the subject;

(b) comparing the CNREB-1 nucleic acid sequences of the test sample to CNREB-1 nucleic acid sequences of a control sample,

wherein an observed alteration or match in a CNREB-1 nucleic acid sequence in the test sample as compared to the CNREB-1 nucleic acid sequences in the control sample, is indicative of the subject's susceptibility to developing a renin-angiotensin system mediated disorder.

62. The method of claim 61, wherein the observed alteration is apparent when a CNREB-1 nucleic acid sequence in the test sample is compared to wild-type CNREB-1 nucleic acid sequences in the control sample.

63. The method of claim 61, wherein the observed match is apparent when a CNREB-1 nucleic acid sequence in the test sample is compared to mutant CNREB-1 nucleic acid sequences in the control sample.

64. The method of claim 61, wherein CNREB-1 mRNA molecules are compared.

65. The method of claim 64, wherein alteration of CNREB-1 mRNA is detected by hybridization of mRNA from the test sample to a CNREB-1 nucleic acid selected from the group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5 and the nucleic acid of SEQ ID NO:6.

66. The method of claim 65, wherein CNREB-1 cDNA sequences are compared, said comparing performed by hybridization of a CNREB-1 cDNA probe to genomic DNA isolated from the test sample.

67. The method of claim 66, further comprising:

(a) subjecting genomic DNA isolated from a test sample of the subject to Southern hybridization with the CNREB-1 cDNA probe; and

(b) comparing the hybridizations of:

(i) the CNREB-1 cDNA probe to a test sample of the subject and (ii) the CNREB-1 cDNA probe to a control sample.

68. The method of claims 66 or 67 , wherein the CNREB-1 cDNA probe detects a restriction fragment length polymorphism.

69. The method of claim 61, wherein CNREB-1 nucleic acid sequences are compared, said comparing being performed by determining the sequence of at least a portion of a CNREB-1 cDNA in the test sample using a polymerase chain reaction,

wherein deviations in the CNREB-1 cDNA determined from that of the wild-type CNREB-1 nucleic acid sequence shown in SEQ ID NO:1, is indicative of the subject's susceptibility to developing a renin-angiotensin system mediated disorder.

70. The method of claim 61, wherein the alteration of CNREB-1 nucleic acid sequences is detected by identifying a mismatch between molecules (a) a CNREB-1 cDNA or CNREB-1 mRNA isolated from the test sample and (b) a nucleic acid probe complementary to the human wild-type CNREB-1 nucleic acid sequence, when molecules (a) and (b) are hybridized to each other to form a duplex.

71. The method of claim 61, wherein CNREB-1 nucleic acid sequences are compared and the alteration of CNREB-1 nucleic acid sequences is detected by the steps of:

(a) amplifying CNREB-1 cDNA sequences in the test sample, and

(b) hybridizing the amplified CNREB-1 cDNA sequences to nucleic acid probes which comprise CNREB-1 sequences.

72. The method of claim 61, wherein CNREB-1 nucleic acid sequences are compared and the alteration of CNREB-1 nucleic acid sequences is detected by molecular cloning of CNREB-1 genes in the test sample and sequencing all or part of the cloned CNREB-1 gene.

73. The method of claim 61, wherein the detection of alteration of CNREB-1 nucleic acid sequences comprises screening for a deletion mutation.

74. The method of claim 61, wherein the detection of alteration of CNREB-1 nucleic acid sequences comprises screening for a point mutation.

75. The method of claim 61, wherein the detection of alteration of CNREB-1 nucleic acid sequences comprises screening for an insertion mutation.

76. The method of claim 61, wherein the test sample is tissue.

77. The method of claim 76, wherein the tissue is selected from the group consisting of brain, heart, breast, colon, bladder, uterus, prostate, stomach, testis, ovary, pancreas, pituitary gland, adrenal gland, thyroid gland, salivary gland, mammary gland, kidney, liver, intestine, spleen, thymus, bone marrow, trachea, and lung.

78. The method of claim 61, wherein the test sample is biological fluid.

79. The method of claim 78, wherein the biological fluid is selected from the group consisting of amniotic fluid, aqueous humor, bile, blood, bronchoalveolar lavage, bronchial fluid, cerebrospinal fluid, follicular fluid, gingival crevicular fluid, middle ear fluid, peritoneal fluid,

pleural fluid, prostatic fluid, saliva, seminal fluid, serum, sweat, synovial fluid, tears, culture supernatant, and urine.

80. A method for modulating c-myc expression in a cell, comprising:

contacting a cell expressing c-myc with an agent that modulates in the cell CNREB-1 activity in an amount effective to modulate c-myc expression in the cell.

81. The method of claim 80, wherein the agent is a nucleic acid.

82. The method of claim 80, wherein the agent is a polypeptide.

83. The method of claim 80, wherein said contacting the cell expressing c-myc with an agent occurs *in vitro*.

84. The method of claim 80, wherein said contacting the cell expressing c-myc with an agent occurs *in vivo*.

85. A method for modulating collagen Type II expression in a cell, comprising:

contacting a cell expressing collagen Type II with an agent that modulates in the cell CNREB-1 activity in an amount effective to modulate collagen Type II expression in the cell.

86. The method of claim 85, wherein the agent is a nucleic acid.

87. The method of claim 85, wherein the agent is a polypeptide.

88. The method of claim 85, wherein said contacting the cell expressing collagen Type II with an agent occurs *in vitro*.

89. The method of claim 85, wherein said contacting the cell expressing collagen Type II with an agent occurs *in vivo*.

90. A method for modulating T cell Receptor expression in a cell, comprising:

contacting a cell expressing T cell Receptor with an agent that modulates in the cell CNREB-1 activity in an amount effective to modulate T cell Receptor expression in the cell.

91. The method of claim 90, wherein the agent is a nucleic acid.

92. The method of claim 90, wherein the agent is a polypeptide.

93. The method of claim 90, wherein said contacting the cell expressing T cell Receptor with an agent occurs *in vitro*.

94. The method of claim 90, wherein said contacting the cell expressing T cell Receptor with an agent occurs *in vivo*.

95. A pharmaceutical composition comprising:

a CNREB-1 inhibitor in a pharmaceutically effective amount to inhibit CNREB-1 activity, and

a pharmaceutically acceptable carrier.

96. The pharmaceutical composition of claim 95, further comprising an adenylate cyclase inhibitor in a pharmaceutically effective amount to inhibit CNREB-1 activity.

97. The method of claims 95 or 96, wherein the CNREB-1 inhibitor is a nucleic acid.

98. The method of claim 97, wherein the nucleic acid is an antisense nucleic acid or a dominant negative nucleic acid of a CNREB-1 nucleic acid selected from the group consisting of the nucleic acid of SEQ ID NO:1, the nucleic acid of SEQ ID NO:3, the nucleic acid of SEQ ID NO:5 and the nucleic acid of SEQ ID NO:6.